

# Predictive utility of NT-pro BNP for infarct size and left ventricle function after acute myocardial infarction in long-term follow-up

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## Abstract.

**PURPOSE:** The aim of the study was to evaluate the utility of N-terminal pro-B-type natriuretic peptide (NT-pro BNP, pg/ml) assessment to predict infarct size and left ventricle function after ST-segment elevation myocardial infarction (STEMI) at long-term follow-up.

**METHODS:** In 45 patients with first STEMI less than 3 hours from symptom onset treated with mechanical reperfusion NT-pro BNP was assessed early (at admission) and at 6 months. Cardiac magnetic resonance (CMR) parameters (delayed enhancement infarct size (IS, %), left ventricular end-diastolic (LVEDVI, ml/m<sup>2</sup>) and end-systolic (LVESVI, ml/m<sup>2</sup>) volume indexes) were assessed at 6 months.

**RESULTS:** No significant correlation was found between baseline NT-pro BNP assessment and IS and left ventricle function after 6 months. There was a significant correlation between 6-month NT-pro BNP and IS ( $r = 0.65$ ,  $p < 0.001$ ) and left ventricle remodeling at 6 months (LVEDVI,  $r = 0.53$ ,  $p = 0.001$ ; LVESVI,  $r = 0.51$ ,  $p = 0.002$ ).

**CONCLUSIONS:** Assessment of NT-pro BNP level 6 months after STEMI remains a good indicator of infarct size and left ventricle function at long-term follow-up.

**Keywords:** ST-elevation myocardial infarction, infarct size, percutaneous coronary intervention, NT-pro BNP, cardiac magnetic resonance

## 1. Introduction

Infarct size is an important prognostic marker with a strong correlation to mortality after ST-segment elevation myocardial infarction (STEMI) [1,2]. Left ventricular function is strongly related to clinical outcome, with increasing mortality rates for left ventricular ejection fraction (LVEF) < 40% [3]. Cardiac magnetic resonance (CMR) imaging is the most precise technique of infarct size assessment with good diagnostic accuracy and reproducibility and allows to detect even small

subendocardial injury [4–6]. The cardiac neurohormone N-terminal pro-B-type natriuretic peptide (NT-pro BNP) is secreted in response to increased left ventricular wall stretch [7], but also myocardial ischemia and infarction may stimulate its excretion [8–10]. The aim of this study was to evaluate the value of NT-pro BNP in prediction of infarct size and myocardial function assessed in CMR 6 months after STEMI.

## 2. Material and methods

### 2.1. Patient population

The study was approved by the Institutional Review Board at the Jagiellonian University Medical College

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in Krakow, Poland. All patients gave informed consent and the study conformed to applicable institutional and national guidelines for research on human subjects, as well as to the Declaration of Helsinki. The inclusion criteria were age over 18 years, STEMI with time from chest pain onset to diagnosis less than 3 hours. STEMI was diagnosed if: chest pain persisted over 30 minutes; there was an ST elevation in J point  $> 0.2$  mV in V2-V3 and  $> 0.1$  mV in other corresponding leads. Main exclusion criteria were: lack of informed consent; prior myocardial infarction; contraindications to lytic therapy; contraindications to PCI (e.g. contrast allergy); advanced neoplasm or other chronic disease with impaired long-term survival; cardiogenic shock; acetylsalicylic acid intolerance or contraindications to clopidogrel. All patients received aspirin (300–500 mg), loading dose of clopidogrel (600 mg), and a bolus of unfractionated heparin (60–100 U/kg). Tenecteplase was given in a weight adjusted standard dose in patients with anticipated delay to PCI longer than 90 minutes. Before PCI activated clotting time was monitored in all patients and unfractionated heparin was added if necessary to maintain optimal anticoagulation. Bare-metal stents were used during primary PCI. In patients with multivessel disease PCI was performed only in the infarct-related artery. Acetylsalicylic acid (75 mg daily) and clopidogrel (75 mg daily) were prescribed at discharge for at least 12 months with other drugs according to patient individual status and guideline recommendations for secondary prevention.

## 2.2. NT-pro BNP analysis

NT-pro BNP was determined in human serum. Samples of blood were obtained on admission to the cathlab and after 6 months. The blood sample collected from the ulnar vein was centrifugated and stored in a refrigerator at  $-85^{\circ}\text{C}$  until final examination. Concentration of NT-pro BNP was determined using automatic Modular Analytics E170 (Roche) analyzer with electrochemiluminescence immunoassay (ECLIA) with two specific polyclonal antibodies against NT-pro BNP.

## 2.3. Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) study was performed on 1.5T scanner (GE Signa EXCITE) with TORSOPA coil. Dedicated software was used for post-processing (MASS, Medis). Analyses were performed by observer blinded to patients' clinical data. Left ventricle volumes, LVEF and infarct size in one

Table 1

Characteristics of the study population. Angiography and PCI characteristics ( $n = 45$ )

Age (years, median)	60.2 (42–77)
Male (%)	77.6
Diabetes (%)	13.6
Arterial hypertension (%)	53.4
Dyslipidemia (%)	44.4
History of smoking (%)	64.3
Killip class $> 1$ (%)	11.5
Time from chest pain onset to PCI (minutes, median and IQR)	223 (87–255)
Infarct related artery (%)	
LAD	34.2
Cx	9.5
RCA	56.2
Multivessel disease (%)	21.1
Lytics (%)	48.8
Abciximab (%)	39.1
Stent implantation (%)	93.3
TIMI 3 after PCI (%)	86.3
TMPG 3 after PCI (%)	67.6
Baseline troponin (ng/ml, median and IQR)	0.71 (0.26–1.93)
Baseline CK (IU/l, median and IQR)	359 (165–780)
Baseline CKMB (IU/l, median and IQR)	47 (20–112)

Cx – circumflex artery; IRA – infarct related artery; LAD – left anterior descending artery; PCI – percutaneous coronary intervention; RCA – right coronary artery; TIMI – Thrombolysis In Myocardial Infarction.

study per patient, minimum 6 months (mean 180 days, range 170–210 days) after index myocardial infarction were analyzed. The end-diastolic and end-systolic volume indices (LVESVI and LVEDVI, ml/m<sup>2</sup>) were obtained after dividing volume by body surface area according to the DuBois formula [11]. Left ventricular volumes and LVEF were assessed with cine-CMR using a steady-state free-precession technique (FIESTA) with the following imaging parameters: 20 phases per slice location, FOV  $32 \times 32$  cm; TR 1.6 ms; TE 2.8 ms; FA  $20\text{--}30^{\circ}$ ; matrix  $256 \times 160$ ; NEX 1. 10–14 consecutive slices of 8 mm were planned in short axis view. Also one horizontal long axis view (four-chamber) was obtained. Delayed enhancement images were acquired 15–20 min after a double bolus of gadolinium (0.2 mmol/kg) using inversion recovery gradient-echo sequence with the following imaging parameters: FOV  $42 \times 42$  cm; TR 8 ms; TE 3.8 ms; FA  $40\text{--}50^{\circ}$ , NEX 2; slice thickness 8 mm. The inversion time was adjusted individually to null normal myocardium. Slice locations of the delayed enhancement images were copied from the cine images to ensure registration between cine-CMR and infarct measurements. The volume of delayed enhancement was quantified manually from consecutive short axis slices and was multiplied by 1.05 g/ml to obtain myocardial infarct mass (1 ml = 1.05 g). Papillary muscles were

Table 2  
Correlations of NTproBNP and infarction size with CK/CKMB/troponin levels at baseline (\* $p < 0.05$ )

	CMR infarct size	CMR LVEF	Baseline NTproBNP	6 months Baseline NTproBNP
CK baseline	$r = 0.196$ ( $p = 0.28$ )	$r = -0.073$ ( $p = 0.68$ )	$r = 0.335$ ( $p = 0.049$ )*	$r = -0.025$ ( $p = 0.89$ )
CK max	$r = 0.862$ ( $p < 0.001$ )*	$r = -0.518$ ( $p = 0.001$ )*	$r = 0.107$ ( $p = 0.53$ )	$r = 0.515$ ( $p = 0.001$ )*
CK MB baseline	$r = 0.182$ ( $p = 0.31$ )	$r = -0.103$ ( $p = 0.56$ )	$r = 0.313$ ( $p = 0.07$ )	$r = -0.035$ ( $p = 0.84$ )
CK MB max	$r = 0.830$ ( $p < 0.001$ )*	$r = -0.488$ ( $p = 0.003$ )*	$r = 0.090$ ( $p = 0.60$ )	$r = 0.483$ ( $p = 0.003$ )*
Troponin baseline	$r = -0.073$ ( $p = 0.70$ )	$r = 0.332$ ( $p = 0.07$ )	$r = 0.354$ ( $p = 0.06$ )	$r = -0.238$ ( $p = 0.20$ )

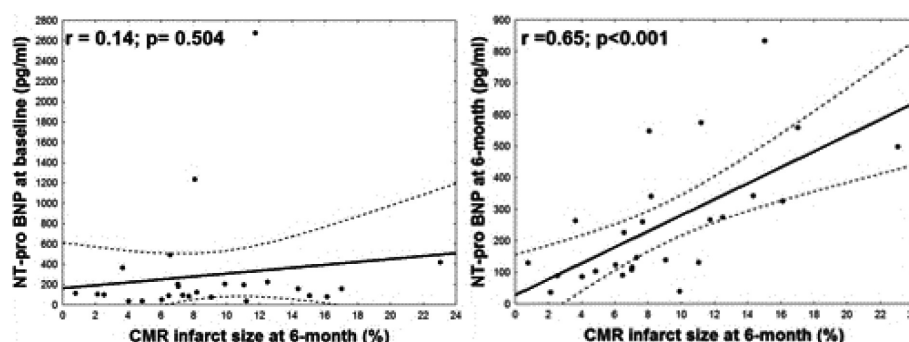


Fig. 1. Spearman correlation between NT-pro BNP values at baseline and after 6 months and infarct size.

not included into the delineations of hyperenhanced area. Infarct size was expressed as percentage of total left ventricular mass.

### 3. Statistical analysis

Results were expressed as medians with interquartile range (IQR) or percentages of patients. Correlations were calculated using Spearman method with the use of two-tailed tests. Receiver-operating characteristic (ROC) curve analysis was performed to calculate sensitivity and specificity of NT-pro BNP value in predicting CMR infarct size after 6 months. Multivariate regression analysis was performed to find significant predictors of CMR infarct size  $\geq 10\%$  and CMR LVEF  $< 40\%$ . Forward selection was used and the probability value for covariates to enter the model were set at 0.10 level. Following covariates were tested: age, gender, presence of diabetes mellitus, arterial hypertension, infarct related artery (LAD vs. non-LAD), infarct related artery patency at baseline (TIMI 0 + 1 vs. 2 + 3), time from symptoms onset to lysis, time from symptoms onset to balloon. A  $p$  value of  $< 0.05$  was considered statistically significant. Statistica 7.0 (Statsoft, Poland) was used to perform statistical analysis.

### 4. Results

A total of 45 patients with STEMI treated with primary PCI were enrolled. Baseline and angiographic

characteristics are presented in Table 1. In 22 patients (48.8%) lytic therapy was administered before transfer to cathlab due to long anticipated delay to PCI. Median levels of NT-pro BNP at admission were 155.4 (79.2–254) pg/ml, after 6 months – 242.2 (108.8–361.3) pg/ml. The CMR study showed infarct size of 8.1 (4.9–12.5)%, LVEF of 43.9 (39.2–52.5)%, LVEDVI of 73.4 (62.3–90.9) ml/m<sup>2</sup> and LVESVI of 39.5 (29.7–54.4) ml/m<sup>2</sup> (all medians with IQR). There was no correlation between baseline NT-pro BNP and CMR infarct size (Fig. 1) and left ventricle function at 6 months (LVEF,  $r = -0.13$ ,  $p = 0.5$ ; LVEDVI,  $r = -0.033$ ,  $p = 0.86$ ; LVESVI,  $r = -0.024$ ,  $p = 0.9$ ). There was a significant correlation of NT-pro BNP and CMR infarct size after 6 months (Fig. 1), LVEDVI ( $r = 0.52$ ,  $p = 0.001$ ) and LVESVI ( $r = 0.54$ ,  $p = 0.002$ ). We also found a trend in correlation between NT-pro BNP after 6 months and LVEF assessed in CMR ( $r = -0.35$ ,  $p = 0.08$ ). Correlations of NT-pro BNP and infarct size with troponin/CK/CKMB levels at baseline were also calculated (Table 2). In receiver-operating characteristic (ROC) curve analysis, the optimal NT-pro BNP at 6 months cut-off value to predict CMR infarct size more than 10% was 134.5 pg/ml with 94% sensitivity and 69% specificity (AUC = 0.88). The optimal NT-pro BNP cut-off value was 264.3 pg/ml with 90% sensitivity and 78% specificity (AUC = 0.8) for predicting LVEF less than 40% at 6 months. The median values of NT-pro BNP for infarct size less and more/equal than 10% and LVEF less and more/equal than 40%

Table 3  
Infarct size according to NT-pro BNP median values (median, IQR)

CMR infarct size (%)	< 10%	≥ 10%	p
NT-pro BNP at baseline (pg/ml)	100.7 (66.6–204)	156 (87.1–367.4)	0.24
NT-pro BNP at 6 months (pg/ml)	106.7 (87.5–177.8)	341 (267.4–555.1)	< 0.001

Table 4  
Left ventricle ejection fraction according to NT-pro BNP median values (median, IQR)

CMR LVEF (%)	≥ 40%	< 40%	p
NT-pro BNP at baseline (pg/ml)	99.2 (74.7–197.9)	189.8 (100.3–980)	0.19
NT-pro BNP at 6 months (pg/ml)	137.8 (102–263.1)	195.2 (271.1–630.2)	0.007

Table 5  
Multivariate regression analysis for CMR infarct size ≥ 10%

Variable	OR (95% CI)	P value
NT-pro-BNP 6 months	1.013 (1.001–1.024)	0.029
Age [per 1 year]	0.857 (0.726–1.011)	0.068
IRA patency at baseline [TIMI 2 + 3 vs. 0 + 1]	0.150 (0.001–0.426)	0.014

Table 6  
Multivariate regression analysis for LVEF < 40%

Variable	OR (95% CI)	P value
NT-pro-BNP 6 months	1.006 (1.000–1.013)	0.044
Age [per 1 year]	0.878 (0.752–1.025)	0.099
Infarct-related artery [LAD vs. non-LAD]	9.534 (0.942–96.480)	0.056

are shown in Tables 3 and 4. Results of multivariate regression analysis are shown in Tables 5 and 6.

## 5. Discussion

In this study NT-pro BNP assessment at 6 month was a good indicator of infarct size and left ventricular function at 6-month follow-up in patients with STEMI. Baseline (admission) NT-pro BNP values did not correlate with any CMR parameters at 6-month. The reason for this finding could be the enrollment criteria regarding early presenters with STEMI < 3 hours from symptom onset and time to PCI 223 minutes (median). The plasma level of BNP increases rapidly but within hours from the onset of acute myocardial infarction (AMI) [12]. The CMR examination was performed after 6 months what allowed to assess infarct zone and ventricular function in rather stable state of scar evolution and remodeling process [13]. Very limited data on BNP and NT-pro BNP and their association with the extent of myocardial infarct size detected by CMR are available. Correlations of BNP with infarct size determined by thallium-201 SPECT [14], technetium-99 m sestamibi SPECT [15], cardiac enzymes [16,17] and CMR have been reported previously, nonetheless, only few studies have focused on the correlation of NT-pro

BNP with infarct size. NT-pro BNP may be superior to BNP in identifying and evaluating cardiac dysfunction [18,19] and therefore its correlation with infarct size and LV function after AMI. Cochet et al. found correlations between NT-pro BNP concentrations on day 3 after AMI and LVEF and infarct size derived from the CMR images [20], but they measured NT-pro BNP in a heterogeneous cohort of patients with acute coronary syndromes and without long-term monitoring. In our study we analyzed a homogenous group of patients with STEMI and early presentation up to 3 hours from symptoms onset. Therefore confounding factors like clinical variety of acute coronary syndromes, ischaemia duration, could be eliminated. Haeck et al. investigated correlation of baseline values of NT-proBNP in presenters below 6 hours from symptom onset with CMR infarct size 4–6 months after AMI [21]. In contrast to our study in patients with non-anterior wall STEMI undergoing primary PCI, an admission NT-pro BNP level was a strong, independent predictor of left ventricular function assessed by CMR imaging at follow-up. Mayr et al. found that NT-pro BNP on day 3 after admission correlates with acute and chronic infarct size and LVEF assessed in CMR on day 6 and 12 months after AMI [22]. The lack of correlation between NT-pro BNP at baseline and left ventricular function or infarct size after 6 months might be due to a contribution of

the ischemic stimulus – resolved later after angioplasty – to an early NT-pro BNP level, which might have obscured the relationship between NT-pro BNP and LV hemodynamics [23].

To the best of our knowledge there was no study previously published demonstrating the relation between baseline and 6-month NT-pro BNP levels with CMR infarct size and CMR left ventricle function after STEMI in very early presenters (< 3 hours from symptom-onset).

## 6. Limitations

The main limitation of the present study is a relatively small number of patients enrolled. This allowed only to analyze surrogate end-points but not clinical end-points. Only one CMR study was performed for each patient so it was impossible to observe time changes of left ventricular parameters.

## 7. Conclusions

Late assessment of NT-pro BNP is a good indicator of infarct size and left ventricle function at 6 months in patients with STEMI.

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